Treatment of rectal chlamydia infection may be more complicated than we originally thought

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Rectal chlamydia diagnoses have been increasing among MSM and may also rise among women as anal sex rates increase among heterosexuals. However, there is growing concern about treatment for rectal chlamydia with treatment failures of up to 22% being reported. This article addresses factors that may be contributing to treatment failure for rectal chlamydia, including the pharmacokinetic properties of azithromycin and doxycycline in rectal tissue, the ability of chlamydia to transform into a persistent state that is less responsive to antimicrobial therapy, the impact of the rectal microbiome on chlamydia, heterotypic resistance, failure to detect cases of lymphogranuloma venereum and the performance of screening tests. If we are to reduce the burden of genital chlamydia, treatment for rectal chlamydia must be efficacious. This highlights the need for randomized controlled trial evidence comparing azithromycin with doxycycline for the treatment of rectal chlamydia.

Keywords: azithromycin, doxycycline, treatment failure

Introduction

Chlamydia trachomatis is the most common bacterial sexually transmitted infection (STI) worldwide with about 100 million adults infected at any point in time.1 In countries that target both men and women for screening, ~40% of cases are among men,2,3 and while these data do not differentiate between rectal, urethral or other sites of infection, available prevalence data suggest that, among MSM, the prevalence of rectal chlamydia is higher than that of urethral infection.4 Rectal chlamydia among women is also of increasing concern with data from the UK showing that 15%–17% of heterosexual people reported anal sex in the last year, a 2–3-fold increase since 1990.5 However, many women acquire rectal chlamydia infection in the absence of any reported anal sex6 and autoinoculation of cervical chlamydia infection from the rectal site has been raised as a potential issue in women.7 As STIs are associated with increasing HIV prevalence,8 effective treatment for rectal infection is important for HIV control.

Current STI treatment guidelines for MSM in the USA recommend treatment of rectal chlamydia with a single 1 g dose of azithromycin,9 but there are increasing concerns about its effectiveness with treatment failures of up to 22% being reported.10 A recent meta-analysis examining rectal chlamydia treatment found a pooled treatment efficacy of ~83% for 1 g of azithromycin and 99% for 100 mg of doxycycline twice daily for 7 days.11 While these results may warrant concern about azithromycin’s effectiveness, the quality of evidence included was poor with no randomized controlled trials (RCTs) directly comparing azithromycin with doxycycline identified.

Pharmacokinetic properties of azithromycin and doxycycline in rectal tissue

Several factors may be contributing to treatment failure for rectal chlamydia. Firstly, it is possible that the bioavailability of azithromycin in rectal tissue is less than that observed in urethral or cervical tissue. Early studies found that azithromycin concentrations were above the MIC for chlamydia in cervical mucus 14 days following a single 1 g dose12 and exceeded the MIC for chlamydia in ‘gynaecological tissue’ for at least 8 days following a 500 mg dose.13 With no pharmacokinetic data evaluating azithromycin in rectal tissue available, it is not known whether the drug reaches effective concentrations in rectal tissue. However, data from a study in 1990 reported lower azithromycin concentrations in gastric mucosa compared with urological and gynaecological tissue, which could imply that concentrations may be lower in rectal tissue.14 Azithromycin has unique pharmacokinetic properties, including its delivery to the site of infection by phagocytic cells (e.g. polymorphonuclear leucocytes) released during the immune response.
to infection.\textsuperscript{15} Data from animal models suggest that the immune response in the gastrointestinal (GI) tract is down-regulated so that chlamydia, like other micro biota in the gut, can remain at the site indefinitely, replicating without being killed by the immune response. If indeed the innate immune response in humans is similarly down-regulated, then it is possible that there will be a reduction in polymorphonuclear leucocytes recruited to deliver azithromycin to the infection site. This is supported by mouse studies that have shown that chlamydiae resident in the GI tract are not as susceptible to clearance by azithromycin as they are in the genital tract.\textsuperscript{7} Further evidence to support a reduced immune response in the GI tract is provided by a recent human study that found a dampened inflammatory response in the rectum in response to chlamydia. Therefore, it is biologically plausible that a reduced local immune response in the rectum may attenuate azithromycin efficacy. It is important to note, however, that other non-immune-related mechanisms, such as passive and active transport systems, also play a role in the delivery of azithromycin to tissues including epithelial cells.\textsuperscript{17}

Unlike azithromycin, doxycycline is highly lipid soluble, which facilitates its rapid absorption into the tissues.\textsuperscript{18} While there are limited data available for the pharmacokinetics of doxycycline in rectal tissue, a double-blind RCT of a single 200 mg dose of doxycycline for prophylaxis in colonic surgery conducted in 1975\textsuperscript{19} found that concentrations of doxycycline in colon and rectal tissue were above the MIC for chlamydia within 4–6 h post-dose. This trial also found that doxycycline accumulated in the mucosal layer of the bowel, where it would be close to the site of infection for rectal chlamydia.\textsuperscript{19} This suggests that doxycycline may be less affected than azithromycin by a down-regulated immune response in the GI tract.

**Chlamydia persistence**

In vitro evidence shows that exposure to adverse conditions (e.g. exposure to β-lactam antibiotics or IFN-γ) and deprivation of iron or amino acids can divert the chlamydia developmental cycle into a persistent state containing enlarged reticulum bodies known as aberrant bodies (ABs). In vitro, ABs are viable, but non-infectious and are semi-refractory to treatment with azithromycin or doxycycline, depending on the cause of persistence. In a recent in vitro study examining the impact of β-lactam antibiotics on chlamydia persistence, all penicillin G-induced ABs with a 95% reduction in chlamydial infectivity. Upon removal of the antibiotics, the chlamydia in humans and it triggers particular immune pathways, which act to starve chlamydia of the essential amino acid tryptophan, leading to the development of ABs. Unlike penicillin-induced persistence, IFN-γ exposure in vitro makes chlamydia more resistant to doxycycline, but still susceptible to azithromycin. It is unclear how often the development of ABs occurs in vivo and whether it is due to either penicillin or IFN-γ exposure, but ABs have been observed in in vivo samples from patients using electron microscopy and found to be less responsive to treatment.\textsuperscript{26} Given that global antibiotic consumption has increased dramatically over the last decade\textsuperscript{20} and STIs such as syphilis, which is treated with penicillin G, have increased dramatically among MSM,\textsuperscript{26} it is plausible that the widespread use of β-lactam antibiotics is inadvertently inducing chlamydia persistence in vivo, making it less susceptible to azithromycin.

**Impact of the rectal microbiome on chlamydia**

The unique microbiome of the rectum is another factor that may make rectal chlamydia more difficult to clear. In vivo, IFN-γ up-regulates the enzyme indoleamine 2,3-dioxygenase, which depletes tryptophan. The genital strains of chlamydia are tryptophan auxotrophs, but have retained the trpBA genes in the tryptophan biosynthesis pathway. This enables them to back-synthesize tryptophan from indole, a compound that is present in the rectum as a product of some bacteria (e.g. *Escherichia coli*).\textsuperscript{27} The availability of indole in the rectum could aid the recovery of chlamydia at this site from ‘attack’ by the host and could therefore influence how well chlamydia responds to treatment and is cleared. While there is ongoing research investigating the role of the microbiome in cervical chlamydia infection, it should also be investigated for its role in sustaining rectal infection.\textsuperscript{28}

**Heterotypic resistance**

Heterotypic resistance has also been proposed as a mechanism for chlamydia treatment failure.\textsuperscript{29} It occurs when the chlamydia infection includes a subpopulation of organisms that is less susceptible to treatment and can be observed in infections with high organism load. As organism load tends to be higher for rectal than urethral infection in men or cervical infection in women,\textsuperscript{30} rectal infections may be more susceptible to heterotypic resistance than other infection sites. It has been suggested that extended doses of azithromycin or doxycycline may improve treatment efficacy in high-organism-load infections.\textsuperscript{29}

**Failure to detect cases of lymphogranuloma venereum (LGV)**

In the absence of genotyping during the initial diagnosis of rectal chlamydia, cases of LGV may be missed, leading to inadequate treatment. LGV is caused by the invasive serovars L1, L2, L2a or L3 of *C. trachomatis* and if infection takes place via the rectal mucosa, it is typically characterized by proctocolitis symptoms.\textsuperscript{31} A longer treatment regimen of 21 days of 100 mg of doxycycline twice daily is the most widely recommended treatment for LGV.\textsuperscript{9} LGV is usually managed on the basis of symptomatic clinical presentation, but there is increasing evidence that LGV can be asymptomatic. An audit of men attending an STI clinic in the Netherlands found that 27% of rectal LGV cases were asymptomatic.\textsuperscript{32} Other smaller studies in the UK and Germany found that between 17% and 53% of cases of rectal LGV among men were asymptomatic.\textsuperscript{33} This data suggest that rectal chlamydia infections in MSM should be genotyped to ensure LGV is diagnosed and treated appropriately. Given the lack of evidence in identifying LGV in women, subtyping for rectal LGV is not currently warranted.

**Performance of chlamydia screening tests**

Lastly, a proportion of rectal chlamydia treatment failure cases diagnosed are likely to be false positives. Nucleic acid amplification
tests are highly sensitive and do not differentiate between live and dead chlamydial nucleic acid, and it has been shown that chlamydia DNA and rRNA can be detected for several weeks after treatment. This highlights the importance of not testing again too quickly after treatment.

Discussion and conclusions

So what does this mean for the treatment of rectal chlamydia infection? As described above, it is biologically plausible that treatment for rectal chlamydia may be less efficacious compared with cervical or urethral infections. We urgently need RCT evidence comparing azithromycin with doxycycline for the treatment of rectal chlamydia. Studies suggest that a longer duration of azithromycin and doxycycline can reduce the development of heterotypic resistance in vivo and can overcome penicillin-induced persistence. Three treatment arms may be needed, comparing a 1 g dose of azithromycin, 100 mg of doxycycline twice daily for 7 days and an extended dose of azithromycin. However, pharmacokinetic data for azithromycin in rectal tissue are urgently needed to inform the extended dose regimen. A pharmacokinetic study investigating azithromycin in blood and leucocytes in humans found that a 1.5 g total dose given over 3 days resulted in greater systemic absorption than the same dose over 5 days, suggesting that shorter treatment courses may be more effective than longer dosing regimens of the same overall total dose. Trials must be double blind and placebo controlled to ensure that the risk of re-infection is similar between treatment arms, because it is possible that taking a daily dose (as is required for doxycycline) may deter people from resuming sexual activity while taking treatment.

In conclusion, rectal chlamydia infection will continue to be a problem in women and men, and until we have good RCT evidence on the optimal treatment regimens, there will continue to be speculation and concern about rectal chlamydia treatment failure.

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